EXHIBIT F

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA

AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO** **WAVE 1 CASES**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

EXPERT REPORT OF SCOTT GUELCHER, PH.D.

The opinions which are held and expressed to a reasonable degree of scientific certainty are as follows:

I. QUALIFICATIONS

Scott Guelcher, Ph.D.

I received my Bachelor's Degree in Chemical Engineering from Virginia Tech in 1992, my Master's Degree in Chemical Engineering from the University of Pittsburgh in 1996, and my Ph.D. in Chemical Engineering from Carnegie Mellon University in 1999. I completed my training as a Post-Doctoral Research Associate in Biomedical Engineering at Carnegie Mellon University in 2005.

I have been an Associate Professor in the Department of Chemical and Biomolecular Engineering at Vanderbilt University since 2012, and prior to that I was an Assistant Professor Department of Chemical and Biomolecular Engineering at Vanderbilt from 2005 through 2012. I was recently appointed a Chancellor's Faculty Fellow for the period 2015 – 2017. In 2015, I taught Process Design and will teach Introduction to Engineering in Fall 2016.

My professional experience includes: Associate Scientist and Senior Associate Scientist at Bayer Corporation, Polyurethanes Division, in South Charleston, West Virginia from 1999-2003; Trainee at Philips Research, in Eindhoven, The Netherlands in 1998; Limited Service Employee at Eastman Chemical Co. from 1995-1997; and Chemical Engineer at Eastman Chemical Co. from 1992-1994.

I am a co-editor of the book, *An Introduction to Biomaterials*, SA Guelcher and JO

Hollinger, eds., Boca Raton: CRC Press 2006. I am also the author of 9 book chapters, including, but not limited to, SA Guelcher, Polyurethanes. In *An Introduction to Biomaterials*, 161 – 183. SA Guelcher and JO Hollinger, eds. Boca Raton, CRC Press 2006; SA Guelcher, Biocompatibility of Injectable Materials. In *Injectable Biomaterials: Science and Applications*. B Vernon, ed. Woodhead Publishing 2011; EM Prieto and SA Guelcher, Tailoring Properties of Polymeric Biomedical Foams. *In Biomedical Foams for Tissue Engineering Applications*. P Netti, ed. Woodhead Publishing 2014; and S. Fernando, M McEnergy, and SA Guelcher, Polyurethanes for Bone Tissue Engineering. In Advances in Polyurethane Biomaterials. J Guan and S Cooper, eds. Woodhead Publishing 2016. My areas of research and interest include biomaterials design and development, drug and gene delivery, tissue engineering, and *in vitro* models for cancer metastasis.

My experience, education and training and a complete list of my published articles are summarized in my Curriculum Vitae attached to this report as Exhibit A. I have published 74 peer-reviewed articles, including two on the design of scaffolds that degrade in response to secretion of reactive oxygen species by infiltrating cells and one on degradation of explanted pelvic mesh. I have given 52 invited presentations and co-authored 176 abstracts presented at scientific meetings, two of which relate to oxidation of polypropylene in biomedical devices. I am a co-inventor on 9 issued U.S. and European Patents and 20 pending applications.

II. SUMMARY OF OPINIONS

This report is an examination and assessment of the polypropylene mesh utilized in devices manufactured by Ethicon to treat Stress Urinary Incontinence (SUI) and pelvic organ prolapse (POP). All of the opinions presented herein are made to a reasonable degree of scientific certainty and within my field of expertise.

1) Polypropylene reacts with molecular oxygen by autoxidation outside the body at elevated temperatures, resulting in chain scission and deterioration in its mechanical properties;

2) After implantation in the body, polypropylene reacts with reactive oxygen species secreted by inflammatory cells, resulting in oxidation, chain scission and mesh embrittlement;

3) The dynamic environment where the polypropylene mesh is implanted coupled with the foreign body reaction leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking;

4) The human body does not stop responding to an implanted mesh, or any frayed particles of mesh released during implantation, unless the product is removed in its entirety;

5) The mesh devices examined for this report are intended to last for the lifetime of the patient, but the presence of antioxidants does not permanently protect the PP against degradation, and thus it is not possible to guarantee that it will perform its intended function after implantation;

6) The effects of oxidation on the stability of Prolene were known to Ethicon prior to launching its SUI and POP devices, but the company did not consider the risks associated with polypropylene oxidation on the stability of Prolene mesh, to the detriment of patients implanted with the devices;

7) Polypropylene mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee; the use of heavy-weight meshes directly correlates with more exposure of polypropylene to the Foreign Body Reaction and greater changes after implantation, which increases the risk of complications.

III. BACKGROUND

Ethicon sells permanently implantable polypropylene-based meshes intended to treat Stress Urinary Incontinence (SUI) and Pelvic Organ Prolapse (POP). All of the products in this litigation use the same Prolene resin to make the polypropylene-based meshes examined in this report.[1] Prolene was developed by Ethicon in the late 1960s for use as a suture material[2] and is more than 97% polypropylene. Additives are blended with polypropylene to modify its properties, including the antioxidants dilauralthiodipropionate (DLTDP) and Santonox-R to protect Prolene during high-temperature processing and long-term storage[3], and the blue pigment copper phthalocyanate (CPC) to enhance its visibility.[4] Prolene resin is manufactured as pellets, which are extruded into monofilaments that are subsequently knit into a specific mesh pattern.[5]

Ethicon's SUI devices consist of their instructions for use (IFU), insertion tools, and a high-density mesh (105 g/m^2) knit from Prolene monofilaments that are 6 mil (0.006 inches) in diameter.[6] The Prosima, Prolift, and Gynemesh POP devices all consist of their IFU, insertion tools, and a lower density mesh (45 g/m^2, known as Gynemesh[7]) knit from Prolene monofilaments that are 3.5 mil (0.0035 inches) in diameter.[8] The mesh used in the Prolift+M POP device is a hybrid material comprising a blend of absorbable Monocryl (poly(glycolide-*co*-ε-caprolactone)) and Prolene. After the Monocryl is absorbed, the density of the remaining Prolene mesh is 28 g/m^2.[9]

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[1] Eth.Mesh.04941016; Eth.Mesh.01310578; Eth.Mesh.03987419; Eth.Mesh.07876572; Eth.Mesh.00019863; Eth.Mesh.0181699
[2] Eth.Mesh.02268619
[3] Eth.Mesh.02268619
[4] *Id*.
[5] ETH.MESH . 03987419; ETH.MESH.01310578
[6] Eth.Mesh.04941016
[7] ETH.MESH.01310578
[8] ETH.MESH.00074499
[9] *Id.*

IV. DISCUSSION

1) Polypropylene reacts with molecular oxygen outside the body by the process of autoxidation

Polypropylene (PP) is a plastic that is formed by a chemical reaction that joins the monomer propylene (which is composed of three carbon atoms and six hydrogen atoms) into a long repeating chain in a process called polymerization.[10] All forms of PP are susceptible to oxidation at the tertiary hydrogen-carbon bond.[11]

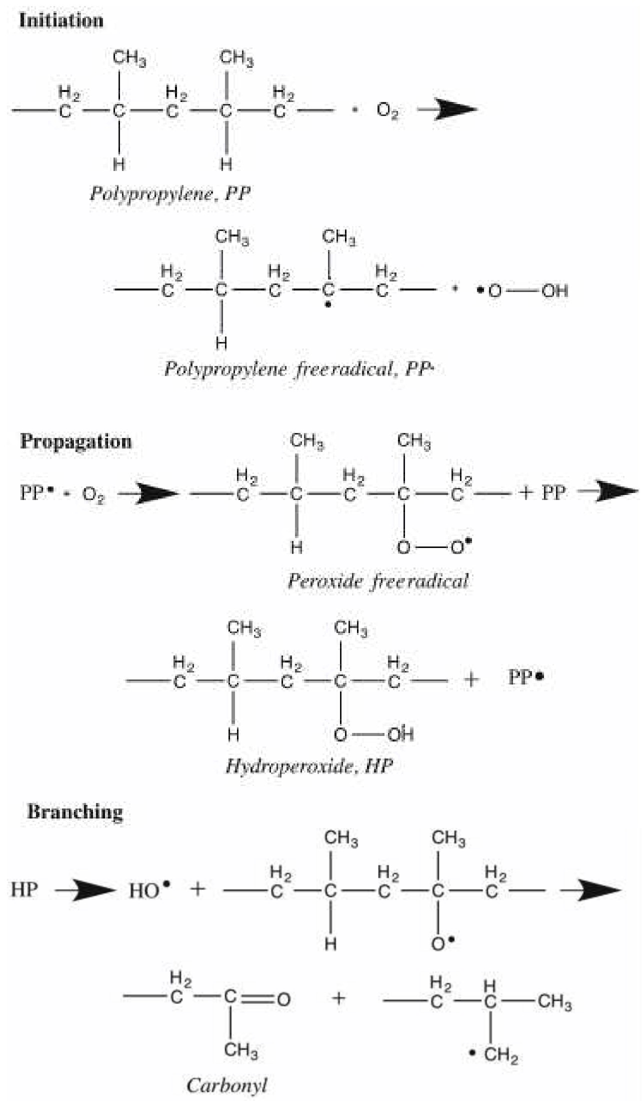

Figure 1. Mechanism of PP autoxidation. Initiation, propagation, and branching reactions lead to chain scission (loss of molecular weight). Products from autoxidation include hydroperoxide and carbonyl groups, which can be detected by analytical methods such as FTIR.

Oxidative attack at the tertiary hydrogen bond is the rate-controlling step in degradation process and results in the PP molecular chain being broken, a process known as chain scission, with the consequent loss in molecular weight. The mechanism of PP autoxidation is shown in Figure 1.[12] The process is autocatalytic, resulting in generation of more PP radicals (PP•) as the reaction progress. Thus, the reaction continues until no more PP can be broken down. The mechanism of PP autoxidation has been investigated extensively since the 1960s and was well known at the time that Ethicon was designing the mesh used in SUI and POP products. As shown in Figure 1, the products of autoxidation include shorter PP chains with carbonyl (C=O) and hydroperoxide (COOH) groups covalently bound to the PP. The presence of these groups can be detected by surface techniques such as

[10] Industrial Polymers, 2008, p. 74.
[11] H.H. Kausch. The effect of Degradation and Stabilization on the Mechanical Properties of Polymers Using Polypropylene Blends as the Main Example. Macromol. Symp. 2005, 225, 165-178.
[12] Reference for Figure 1: C Maier, T Calafut. Polypropylene: The Definitive User's Guide and Databook. Norwich, NY: Plastics Design Library, 1998.

FTIR and x-ray photoelectron spectroscopy (XPS) as evidence of oxidation.[13]

As shown in Figure 2, heat and UV radiation accelerate oxidation of PP.[14] Absorption of oxygen is diffusion-controlled, and the amor e the most accessible to diffusion of O_2. Th - crystallizable segments of the PP chains a o neighboring crystalline domains. Since the tc e molecules, cutting of the tie molecules (r contributing to embrittlement. The key featur t of molecular weight loss that is critical for n Figure 3.[15] An important finding from this st r (~150 hours) than the induction time (~250 f carbonyl groups and hydroxyl groups associ r these conditions. Thus, the induction time overestimates the useful life of PP with respect to its mechanical properties.

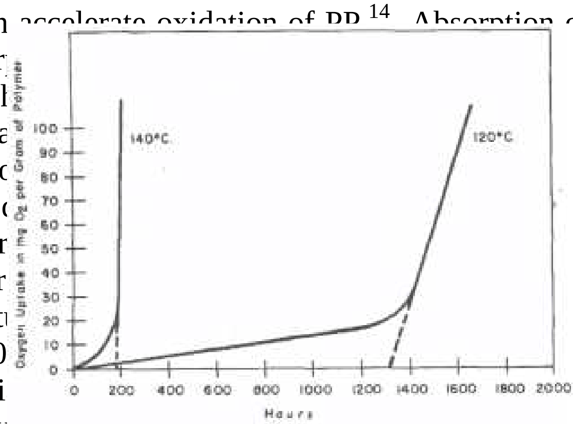

Figure 2. Autoxidation of PP is accelerated at elevated temperatures. Oxygen absorption of stabilized PP increases with time and temperature in 100% O_2. The induction time is determined by extrapolating the autocatalytic constant rate portion of the curve (steeper slope) to the x-axis (dashed line). Reproduced from Oswald and Turi 1965.

The storage stability of unstabilized PP at ambient conditions has also been studied (Figure 4). When PP films were stored at room temperature and atmospheric O_2 concentration, the molecular weight (as measured by intrinsic viscosity) of PP dramatically decreased at 500 days (1.4 years).[16] Thus, while oxidation is accelerated at elevated temperatures and oxygen concentrations (Figure 2), even at ambient temperature and atmospheric oxygen concentration there is chain scission and molecular weight loss.

2) After implantation in the body, polypropylene reacts with reactive oxygen species secreted by inflammatory cells, resulting in oxidation, chain scission and mesh embrittlement;

Liebert et al.[17] (1976) reported the oxidation of unstabilized PP filaments in vivo in a subcutaneous implantation model in hamsters. An induction time of 108 days was determined based on FTIR measurements of hydroxyl (which includes the hydroperoxide COOH) and carbonyl groups. FTIR measurements of hydroxyl and carbonyl groups showed behavior similar to that observed by Fayolle (Figure 3), consistent with the oxidation mechanism. However, Liebert estimated that the induction time for oxidation under *in vivo* conditions (37°C in 3.3% O_2) is approximately 20 years, which is dramatically higher than the measured value of 108 days. The authors suggested that enzymes or other chemicals secreted by cells accelerate the oxidation reaction. Recent papers have shown that this shorter induction time can be explained by the secretion of reactive oxygen species (ROS) by inflammatory cells near the PP fibers that oxidize and degrade the PP fibers *in vivo*.

[13] Fayolle et al. Oxidation-induced embrittlement in polypropylene – a tensile testing study. Polym Degrad Stability 70:333-40, 2000.
[14] HJ Oswald and E. Turi. The Deterioration of Polypropylene by Oxidative Degradation. Polymer Engineering and Science, 1965.
[15] Fayolle et al. Oxidation-induced embrittlement in polypropylene – a tensile testing study. Polym Degrad Stability 70:333-40, 2000.
[16] HJ Oswald and E. Turi. The Deterioration of Polypropylene by Oxidative Degradation. Polymer Engineering and Science, 1965.
[17] Liebert et al. Subcutaneous implants of PP filaments. JBMR 10:939-51, 1976

Upon implantation, the body recognizes PP mesh as a foreign body, which elicits an inflammatory response known as the foreign body reaction.[18] In the early stages, mononuclear cells migrate to the surface of the PP fibers, where they can adhere and participate in the events of the foreign body reaction (Figure 5). Adherent macrophages on the surface of the implanted biomaterial fuse to form foreign body giant cells (FGBCs). Adhesion of macrophages and FBGCs at the biomaterial surface results in an isolated microenvironment between the surface of the biomaterial and the plasma membrane of the cell.[19] In a process known as frustrated phagocytosis, macrophages and FBGCs secrete reactive oxygen species (ROS), acids, and enzymes into this micro-environment. Consequently, the surface of the biomaterial is exposed to high concentrations of ROS, and the chemical composition of the biomaterial will determine its susceptibility to oxidative degradation. As an example, the polyether soft segment of poly(ether urethane)s is known to undergo oxidative degradation. The morphological progression of the foreign body reaction on a poly(ether urethane) surface is shown in Figure 6.[9]

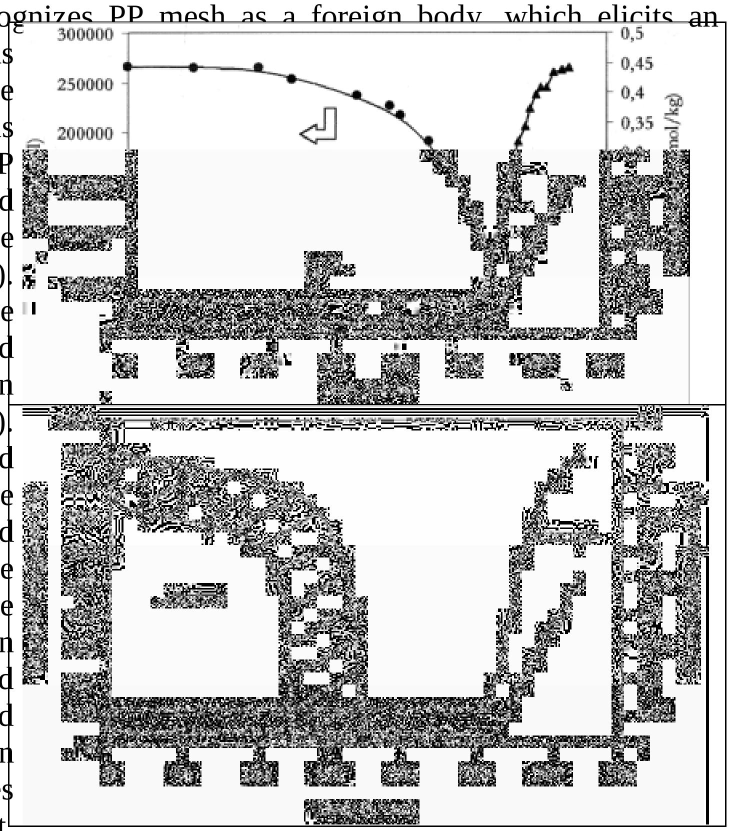

Figure 3. Degradation of unstabilized PP. (A) Molecular weight decreases with time when exposed to oxygen at elevated temperatures (Fayolle et al. 2000). On the right y-axis, the concentration of hydroxyl (triangles) and carbonyl (squares) groups are shown. (B) Evolution of ultimate elongation (diamonds) and hydroxyl (triangles) and carbonyl (squares) groups during exposure to oxygen at elevated temperatures (Fayolle et al. 2000).

[18] James M. Anderson, Analiz Rodriguez, and David T. Chang. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.
[19] *Id.*

While initial studies identifying adherent macrophages and FBGCs as sources of ROS focused on poly(ether urethane)s, these cell populations have also been reported to infiltrate PP mesh.[20] In a recent study characterizing the foreign body reaction of PP implants in a rat abdominal wall model, macrophages and foreign body giant cells were observed both in the tissue surrounding the implant and also the implant itself.[21] Thus, within one week after implantation PP mesh was colonized by macrophages and FBGCs. Furthermore, PP mesh samples showed more inflammatory cells than PP sutures. The hernia literature also provides evidence that the foreign body reaction alters PP *in vivo*. In a study evaluating non-degradable meshes explanted from 17 patients that had surgery for repair of abdominal wall defects, a foreign body reaction characterized by granulation tissue and inflammatory cells 3 – 24 months post-implantation was seen.[22] The authors observed that inflammation near synthetic materials implanted in the abdominal wall persists for years. They further noted that this persistent foreign body reaction can lead to long-term complications, and that further studies are required to evaluate the long-term response of the host tissue to the implanted synthetic graft. Costello et explanted PP hernia mesh a observed degradation of PP fi with the oxidation of PP medi cells during the foreign body rea

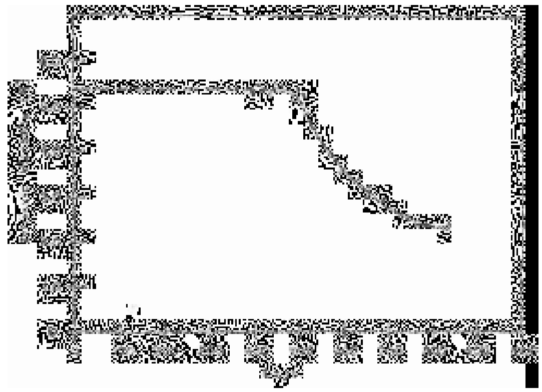

Figure 4. Stability of unstabilized PP at room temperature. Significant molecular weight loss occurs at 500 days. Reproduced from Oswald and Turi 1965.

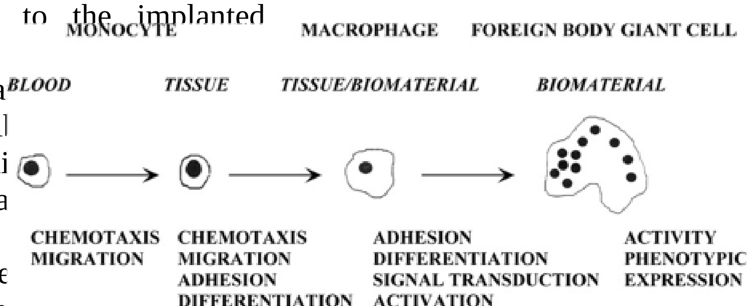

Figure 5. *In vivo* transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign body giant cell at the tissue/biomaterial interface. There is ongoing research to elucidate the biological mechanisms that are considered to play important roles in the transition to foreign body giant cell development. From Anderson et al. Seminars in Immunology 2008.

Three key studies publishe characterize the host inflammatory response to implanted PP provide further evidence that PP mesh undergoes oxidative degradation *in vivo*. Gynemesh PS and UltraPro, which are Prolene meshes used in Ethicon's POP products, were implanted in rhesus macaques by sacrocolpopexy

[20] Celine Mary, Yves Marois, Martin W. King, Gaetan Laroche, Yvan Douville, Louisette Martin, Robert Guidoin, Comparison of the In Vivo Behaviour of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery, ASAIO Journal, 44 (1998) 199-206; VV Iakovlev, ET Carey, J Steege. Pathology of Explanted Transvaginal Meshes. Int. J. Medical, Health, Pharmaceutical and Biomedical Eng. 8(9):510-513, 2014

[21] Tensile strength and host reponse towards different PP implant materials used for augmentation of fascial repair in a rat model. Deprest et al. Int Urogynecol J 18:619-26, 2007.

[22] Foreign Body Reaction to Meshes Used for the Repair of Abdominal Wall Hernias. U. Klinge,1,3 B. Klosterhalfen,2,3 M. Mu¨ller1 and V. Schumpelick1. Eur J Surg 1999; 165: 665–673

[23] C.R. Costello, S.L. Bachman, B.J. Ramshaw, S.A. Grant, Materials Characteriza- tion of Explanted Polypropylene Hernia Meshes, J. Biomed. Mater Res. Part B Appl. Biomat 83 (2007) 44e49; and C.R. Costello, S.L. Bachman, S.A. Grant, D.S. Cleveland, T.S. Loy, B.J. Ramshaw, Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient, Surg. Innov. 14 (2007) 168e176

after an abdominal hysterectomy.[24] After 12 weeks implantation time, the vagina-mesh tissue complexes were harvested and processed for histological and immunohistochemical analysis. Explanted Gynemesh PS and UltraPro meshes showed evidence of a foreign body reaction characterized by a dense mononuclear cell infiltrate near the surface of the mesh fibers. Mononuclear cells staining positive for the pan-macrophage marker CD68 were the cell type present at the highest density adjacent to the mesh fibers. The inflammatory response to all implanted PP meshes was characterized primarily by activated, pro-inflammatory M1 macrophages (Figure 7, Top Left).[25] The ratio of regenerative M2 macrophages to M1 macrophages was higher for the lower density UltraPro mesh compared to the higher density Gynemesh PS. This finding is consistent with the mesh burden concept that the magnitude of the foreign body reaction increases with the amount of mesh in contact with host tissue. Thus, the work by Moalli et al. establishes that the foreign body reaction to implanted PP mesh is dominated by pro-inflammatory M1 macrophages. In a study I co-authored with Dr. Vladimir Iakovlev in 2015, we examined 164 explanted PP pelvic meshes by microscopy.[26] Examination of histological sections revealed the presence of inflammatory cells near the surface of PP fibers, and staining for the oxidative enzyme myeloperoxidase expressed by adherent inflammatory cells was positive on the surface of the degraded layer of the PP fibers (Figure 7, Bottom Left). Another study published in 2015 confirmed that the foreign body reaction to implanted PP mesh results in oxidative degradation of the mesh.[27] PP pelvic meshes explanted from 11 patients were characterized by FTIR, GPC, SEM with energy-dispersive x-ray spectroscopy (EDS), TEM, and TGA and compared to meshes that had not been implanted. FTIR spectra of explanted PP mesh showed broad peaks centered at 3400 cm^{-1}, which correspond to hydroxyl and peroxide groups, and at 1700 – 1750 cm^{-1}, which correspond to carbonyl groups associated with ketones, aldehydes, and carboxylic acids. Importantly, this study demonstrated that oxidized PP, which does not contain nitrogen, and biological material, which does contain nitrogen, could be distinguished by a combination of EDS and SEM. Regions of PP fibers with transverse cracks that were free of biological material were found to contain oxidized PP (Figure 7 Right). Furthermore, clean PP fibers that showed no evidence of transverse cracking revealed evidence of PP oxidation.

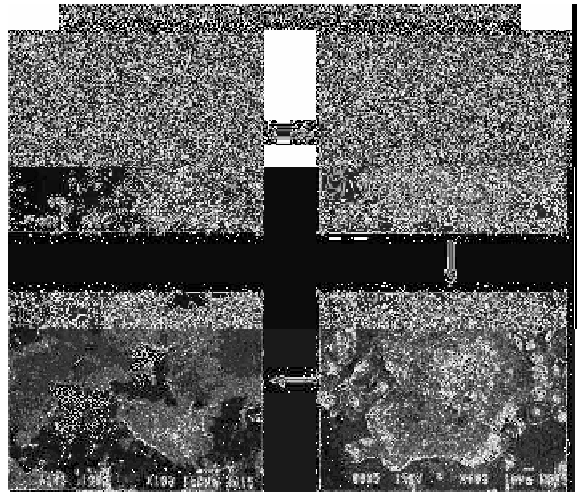

Figure 6. Scanning electron microscopy images of an Elasthane 80A Polyurethane surface from an in vivo cage study showing the morphological progression of the foreign body reaction. The sequence of events at the Polyurethane surface includes (A) monocyte adhesion (0 days), (B) monocyte-to-macrophage development (3 days), (C) ongoing macrophage-macrophage fusion (7 days), and (D) foreign body giant cells (14 days).. From JM Anderson et al., Foreign body reaction to biomaterials. Seminars in Immunology 20:86-100, 2008.

[24] Moalli et al., Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque. Am J Obstet Gynecol. 2015 Nov;213(5):668.e1-668.e10;

[25] JM Anderson et al., Foreign body reaction to biomaterials. Seminars in Immunology 20:86-100, 2008

[26] VV Iakovlev, SA Guelcher, R Bendavid. *In vivo* degradation of polypropylene: microscopic analysis of meshes explanted from 130 patients. *Journal of Applied Biomedical Materials Research B: Applied Biomaterials*, 2015 Aug 28 doi: 10.1002/jbm.b.33502

[27] A Imel, T Malmgren, M Dadmun, S. Gido, J Mays. In vivo oxidative degradation of polypropylene pelvic mesh. Biomaterials 73:131-141, 2015.

Taken together, these findings are consistent with the early observations of Liebert et al. and the scientific principles of the foreign body reaction. Implanted PP mesh is infiltrated by inflammatory cells, which are predominantly M1 pro-inflammatory macrophages. Macrophages in close proximity to the PP fiber surface secrete ROS, resulting in oxidation of the PP fibers. Consequently, the foreign body response to PP is elevated when more PP is present. As noted below, this principle has been acknowledged by Ethicon employees and consultants, who have noted that heavy-weight meshes like the Gynemesh and TVT induce a greater foreign body reaction than light-weight meshes.

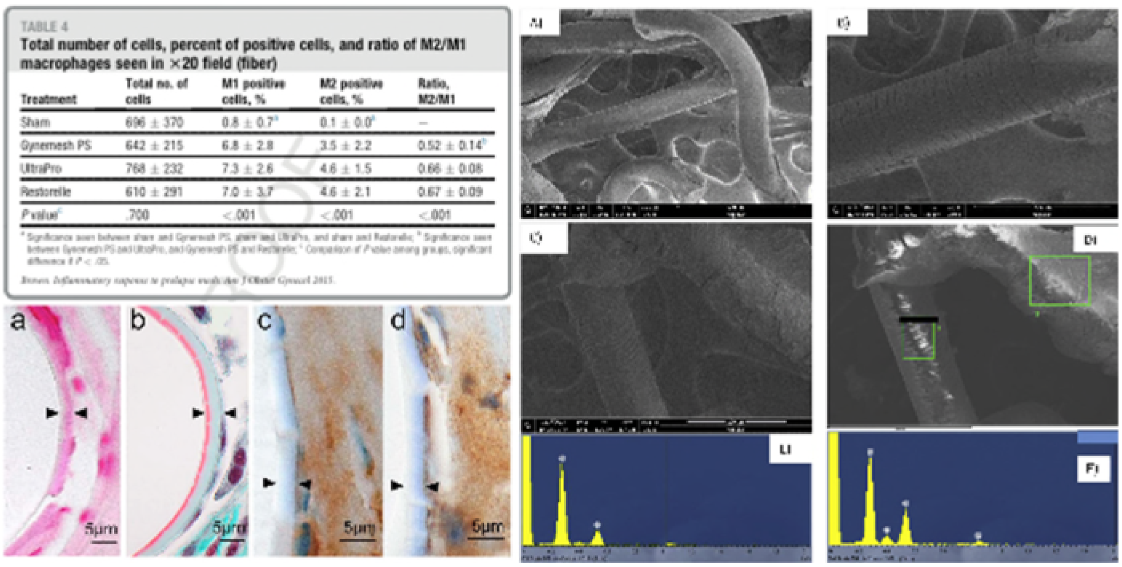
TABLE 4

Total number of cells, percent of positive cells, and ratio of M2/M1 macrophages seen in ×20 field (fiber)

Treatment	Total no. of cells	M1 positive cells, %	M2 positive cells, %	Ratio, M2/M1
Sham	696 ± 370	0.8 ± 0.7[a]	0.1 ± 0.0[a]	–
Gynemesh PS	642 ± 215	6.8 ± 2.8	3.5 ± 2.2	0.52 ± 0.14[b]
UltraPro	768 ± 232	7.3 ± 2.6	4.6 ± 1.5	0.66 ± 0.08
Restorelle	610 ± 291	7.0 ± 3.7	4.6 ± 2.1	0.67 ± 0.09
P value[c]	.700	< .001	< .001	< .001

[a] Significance seen between sham and Gynemesh PS, sham and UltraPro, and sham and Restorelle; [b] Significance seen between Gynemesh PS and UltraPro, and Gynemesh PS and Restorelle; [c] Comparison of *P* value among groups, significant difference if *P* < .05.

Figure 7. Oxidative degradation of PP mesh *in vivo*. Top Left: Table listing the total number of cells, percent of positive cells, and ratio of M2/M1 macrophages seen in x20 field (fiber) (Moalli et al., Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque.) Bottom Left: Additional stains of PP mesh, all images taken with 100x oil immersion objective and cropped to a different magnification, polypropylene degrada-tion layer is pointed between arrowheads: (a) Von Kossa stain is negative for calcium in the brittle "bark" (would stain calcium black), (b) trichrome stain shows that the deeper parts of the "bark" have smaller staining porosity (red) than those close to the surface (green) which correlates with TEM findings [Figure 6(b)], (c) immunohistochemical stain for immunoglobulin G (IgG, stained brown). IgG is present in almost all human tissues and fluids. It is deposited on the surface of degraded polypropylene but is not mixed within it. (d) Immunostain for the oxidizing enzyme of inflammatory cells myeloperoxidase (stains brown). (VV Iakovlev. *In vivo* degradation of polypropylene: microscopic analysis of meshes explanted from 130 patients.) Right: A) SEM of explanted Pinnacle Mesh fibers [XP-7]. B) SEM of explanted Pinnacle Mesh fibers [XP-7]. C) SEM of explanted Pinnacle Mesh fibers [XP-7]. D) SEM image with regions selected for EDS. E) EDS Spectra from region 1 in D. F) EDS Spectra from region 2 in D. (A Imel, T Malmgren, M Dadmun, S. Gido, J Mays. In vivo oxidative degradation of polypropylene pelvic mesh, Biomaterials, 2015.).

3) The dynamic environment where the Prolene mesh is implanted coupled with the foreign body reaction leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking;

In an early study, Prolene sutures implanted for 1 – 2 years in a canine thoracoabdominal bypass model showed evidence of transverse cracks and peeling (Mary 1998).[28] Several more recent studies have reported degradation of explanted PP pelvic mesh. In the first study characterizing explanted pelvic mesh, Clavé et al. reported that 42% of the explants

[28] Celine Mary, Yves Marois, Martin W. King, Gaetan Laroche, Yvan Douville, Louisette Martin, Robert Guidoin, Comparison of the In Vivo Behaviour of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery, ASAIO Journal, 44 (1998) 199-206

showed evidence of chronic inflammation, characterized by an infiltrate of mononuclear cells and FGBCs. SEM analysis revealed that the implants were degraded, and that degradation was observed in meshes that had been implanted for at least 3 months.[29]

In the study that I co-authored with Dr. Iakovlev[30], a layer of degraded PP was observed by optimal microscopy near the surface of the fibers in the explanted mesh (Figure 7). Micro-cracks were present in the degraded PP layer. Degradation and cracking of the polypropylene fibers was observed as early as 18 months for a cohort of 23 explanted PP SUI devices.

Mays et al. also observed degradation of fiber in explanted PP mesh using SEM. Using a combination of SEM and EDS, the authors were able to distinguish between fibers that were clean and those that were coated with biological material. Explanted fibers were observed that showed evidence of severe transverse cracks (Figure 7), which was accompanied by oxidative degradation of the fibers. The authors identified the mechanism of PP degradation as comprising the following steps: infiltration of inflammatory cells that secrete ROS in close proximity to the PP mesh fibers, oxidative degradation of the PP fibers characterized by the appearance of hydroxyl and carbonyl groups in the FTIR spectra, a reduction in molecular weight, embrittlement, cracking, and fragmentation of the PP fibers.

4) PP mesh is known to fray under tension and release particles while being handled and implanted. The human body does not stop responding to these particles or to the PP mesh unless the product is removed in its entirety

As an example of how oxidation of an implanted biomaterial affects its performance, poly(ether urethane)s (PEUs) were used as pacemaker lead insulation due to their improved mechanical properties as compared to silicone rubber. While PEU elastomers were believed to be biocompatible for many years, they are now known to undergo environmental stress cracking due to oxidative degradation of the polyether component and subsequent loss in molecular weight.[31] Adherent macrophages and FBCGs were shown to be responsible for environmental stress cracking. Thus oxidative degradation and environmental stress cracking comprise a vicious cycle in which oxidative degradation drives the embrittlement of the polymer surface and its subsequent cracking, which in turn exposes new surfaces of the material to oxidative degradation. Another study has shown that ROS actively degrades lysine-derived poly(ester urethane)s *in vivo* by an oxidative mechanism.[32] Thus, oxidative degradation of biomaterials *in vivo* in response to ROS secreted by inflammatory cells is well known.

Since the foreign body reaction is present at the biomaterial surface for the lifetime of the

[29] Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261-270
[30] VV Iakovlev, SA Guelcher, R Bendavid. In vivo degradation of polypropylene: microscopic analysis of meshes explanted from 130 patients. Journal of Applied Biomedical Materials Research B: Applied Biomaterials, 2015 Aug 28 doi: 10.1002/jbm.b.33502
[31] *Id.*
[32] AE Hafeman, KJ Zienkiewicz, AL Zachman, HJ Sung, LB Nanney, JM Davidson, SA Guelcher. Characterization of degradation mechanisms of biodegradable lysine-derived aliphatic polyurethanes. Biomaterials 32(2):419-29, 2011. See also Martin, MK Gupta, JM Page, F Yu, JM Davidson, SA Guelcher, CL Duvall. Synthesis of a Porous, Biocompatible Tissue Engineering Scaffold Selectively Degraded by Cell-Generated Reactive Oxygen Species. Biomaterials 35(12):3766-76, 2014.

implant, the oxidative process is ongoing as long as the implant is present.[33] Considering the ongoing foreign body reaction as well as the known susceptibility of PP to oxidation, the mechanical and physical properties of Ethicon's PP mesh will change after it is implanted.

In addition, the properties of Ethicon's PP mesh have been shown to change under tension and while the mesh is being handled.[34] The medical literature and Ethicon's internal studies have reported that particles are lost or shed from the TVT mesh while it is in the box and while it is being implanted.[35] The foreign body reaction to shed particles will be similar to that for the TVT mesh. The body will not stop responding to any particles that are shed inside the body during implantation until those particles are removed in their entirety.

5) **Ethicon's pelvic meshes are intended to last for the lifetime of the patient, but the presence of antioxidants does not permanently protect the PP against degradation, and thus it is not possible to guarantee that these meshes will perform their intended function after implantation.**

Although PP can never be considered inert, it is stabilized against oxidation by adding antioxidants to the molten polymer, which are intended to act as scavengers that will react with oxidative species.[36] The enduring nature of the foreign body reaction emphasizes the need for antioxidants to be added to biomaterials such that the time to oxidation, degradation, and embrittlement is extended.[37] PP in its pure (i.e., unstabilized) form degrades rapidly *in vivo*, with an induction period of only 108 days[38], and carbonyl groups were detected in unstabilized PP by infrared spectroscopy within 50 – 90 days.[39] Liebert et al. also tested stabilized PP in the hamster subcutaneous implant model. Oxidation of stabilized PP was observed, but the experiment ended at 100 days, at which time induction had not been observed for stabilized PP filaments. Consequently, the eventual *in vivo* induction time for stabilized PP has not been reported.

Stabilization with antioxidants is not permanent, since the purpose of using antioxidants is to react with any oxidative species (such as ROS) to prevent their reaction with PP.[40] These stabilizers are distributed throughout the PP, however, and can only protect the polymer if they are in the proper location and only until they are exhausted. The antioxidant package must be optimized for the intended use to achieve maximum service life of the polymer. Neither the Santonox R nor the dilauralthiodipropionate (DLTDP) antioxidant in the Prolene resin used to manufacture Prolene mesh [41] is designed to protect against the ROS secreted by inflammatory cells *in vivo.* Santonox R is a hindered phenolic antioxidant

[33] Foreign Body Reaction to Biomaterials. James M. Anderson, Analiz Rodriguez, and David T. Chang. Semin Immunol. 2008 April ; 20(2): 86–100.
[34] ETH.MESH.01813975; ETH.MESH.01317515; ETH.MESH.03905472; ETH.MESH.00541379; ETH.MESH.00863391.
[35] *Id*.
[36] E. Rene de la Rie. Polymer Stabilizers. A Survey with Reference to Possible Applications in the Conservation Field. Studies in Conservation 33(1988) 9-22
[37] James M. Anderson, Analiz Rodriguez, and David T. Chang. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.
[38] Liebert et al. Subcutaneous implants of PP filaments. JBMR 10:939-51, 1976.
[39] *Id*.
[40] *Id*.
[41] Eth.Mesh.02268620

designed to protect Prolene during high-temperature processing (compounding and extrusion), while DLTDP is designed to protect Prolene from oxidation during long-term storage. Because *in vivo* oxidation and degradation are ongoing in response to the foreign body reaction, the antioxidant will eventually be depleted, resulting in oxidation and degradation of the PP mesh and changes to its properties over time. This cycle of depletion of antioxidants through reaction with ROS followed by the eventual degradation of the surface of the mesh will not stop until all of the mesh is removed, since cracking exposes new surfaces to ROS and the reaction begins anew.[42]

6) The effects of oxidation on the stability of Prolene were known to Ethicon prior to launching its SUI and POP devices, but the company did not consider the risks associated with polypropylene oxidation on the stability of Prolene mesh, to the detriment of patients implanted with the devices.

Ethicon first reported evidence of Prolene oxidation and degradation in internal documents from the 1980s. These documents report evidence of chronic inflammation, oxidation, and degradation (micro-cracking) of Prolene sutures similar to that published in the scientific literature described above. Several relevant studies are reviewed in greater detail below.

In 1981, the depth of surface cracks was measured for explanted cardiovascular and ophthalmic Prolene sutures.[43] The crack depth varied from 0.5 – 4.5 microns. Another memo in 1983 reported cracking of explanted Prolene sutures.[44] One of the explanted sutures showed only 54% of its original strength. The memo noted that the histological evaluation of explanted sutures was consistent with previous studies, characterized by a foreign body reaction and a "degraded acellular infiltrate." This document also refers to a Prolene Microcrack Committee. Thus, Ethicon was sufficiently aware of Prolene surface cracking to form a committee to investigate the mechanism of cracking.

Two memos written in 1984 investigated the cause of microcracking of explanted PP sutures from both ophthalmic and cardiovascular applications[45]. Sutures that were in the body for more than two years exhibited surface or severe transverse cracks. The thickness of the crack layer ranged from 2 – 5 microns thick. Dr. Peter Moy recognized in a November 5, 1984 report that "oxidative degradation is another mechanism through which transverse cracks may be produced on oriented fibers."[46] In an attempt to reproduce the observed cracking *in vitro*, Prolene sutures were incubated in aqueous 30% hydrogen peroxide for up to 1 year. Despite the fact that transverse cracks were not observed, infrared spectroscopy revealed evidence of oxidation products, which prompted Dr. Moy to note that "the possibility of a highly specific *in vivo* oxidation process remains." These findings are consistent with the foreign body reaction, which produces ROS stronger than hydrogen peroxide[47]. If treatment with 30% hydrogen peroxide caused oxidation of the PP suture (as reported by Dr. Moy), then ROS secreted by adherent macrophages would also be expected to cause oxidation. Dr. Moy also cited thermal stability and electron microdiffraction data supporting his hypothesis that at least a portion of the cracked layer contained protein. He recommended that an additional study was necessary to test this

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[42] James M. Anderson1,2,*, Analiz Rodriguez1,*, and David T. Chang2. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.
[43] Eth.Mesh.12831405.
[44] Eth.Mesh.15955438-15955473.
[45] ETH.MESH.15958452, ETH.MESH.15406978, ETH.MESH.15958470
[46] ETH.MESH.1595843
[47] Zhao AH, McNally AK, et al.Human plasma ð2-macroglobulin promotes in vitro oxidative stress cracking of Pellethane 2363-80A: In vivo and in vitro correlations. J Biomed Mater Res (1993) 27: 379-389

hypothesis by performing TEM analysis of known oxidized Prolene samples. Another memo dated November 13, 1984, reported that Prolene microcracks were evaluated by Attenuated Total Reflectance (ATR) and FTIR.[48] These studies found that the cracked Prolene surface is a composite of oxidized polypropylene and adsorbed protein. Surface protein was removed with Soluene treatment, but adsorbed protein remained in the microcracks. Thus, the November 13, 1984 memo by Dan Burkley concludes that the cracked layer contained both oxidized Prolene as well as protein.

In 1985, a series of experiments was proposed, including microscopic FTIR, TEM, and histology, to determine the clinical functionality of cracked sutures, the cracking mechanism, and effects of antioxidant concentration.[49] Dr. Moy further noted that laboratory experiments had not yet replicated the cracking observed in explants, and proposed a systematic evaluation of explanted Prolene sutures.

In 1987, Professor Guidoin provided Ethicon with his explanted sutures, which had been cleaned using a bleach solution as explained in Mr. Burkley's laboratory notebook.[50] SEM images of sutures explanted after 8 years revealed evidence of severe cracking. Another cohort of explanted sutures was scraped with a needle and the scrapings tested by calorimetry and FTIR. The waxy scrapings showed a melting point of 147 – 156^{o}C, which is comparable to that of degraded Prolene. Non-degraded Prolene melts over the range 155 – 165^{o}C. Scrapings were also melted on a KBr window to obtain FTIR spectra, which showed peaks associated with β-keto esters known to be formed during PP oxidation. Mr. Burkley noted in his notebook and memo that "no protein species or peptide bonds were suggested." A memo reporting on a follow-up meeting confirmed the findings that no protein was found on the surface and that Prolene degradation occurred on the surface of the fibers.[51] Several follow-up studies were proposed, including investigating the relationship between antioxidant concentration and polypropylene degradation and cracking. However, to my knowledge these studies were not performed.

In 1991, a 91-day rat subcutaneous implantation study was performed to assess the tissue reaction for several PP-based surgical meshes, including the Prolene mesh used in the SUI and POP devices.[52] All meshes, including Prolene and Prolene Soft, showed evidence of chronic inflammation at 7 and 91 days. Drs. Barbolt and Hutchinson concluded that all meshes showed evidence of a mild inflammatory reaction and infiltration of connective tissue. Furthermore, images of histological sections revealed evidence of adherent macrophages on the surface of the Prolene fibers.

As noted above, Ethicon researchers sought to replicate the surface cracking of Prolene sutures in an *in vitro* experiment. In the 1990s, the effects of the foreign body reaction on biomedical implants were first elucidated. All implantable medical devices are susceptible to the dynamic nature of the environment in which they are implanted. Environmental stress cracking of implanted biomaterials is controlled by three factors: (1) residual stress in the biomaterial, (2) a source of chemical degradation in the body, and (3) the chemical structure of the biomaterial.[53] Poly(ether urethane)s used as pacemaker lead insulation are an example of how oxidation of an implanted biomaterial can lead to Environmental Stress

[48] ETHMESH15958336
[49] ETHMESH15958445
[50] Eth.Mesh.00000367, Eth.Mesh.12831391
[51] Eth.Mesh.12831407
[52] Eth.Mesh. 02319001, eth.mesh.01425079
[53] Anderson et al. Cellular interactions with biomaterials: in vivo cracking of pre-stressed Pellethane 2363-80A. JBMR 24: 621-37, 1990.

Cracking (ESC) and device failure. While poly(ether urethane) elastomers were believed to be biocompatible for many years, they are now known to undergo ESC due to oxidative degradation of the polyether component and subsequent loss in molecular weight.[54] As shown in Figure 8, adherent macrophages and FBCGs were responsible for environmental stress cracking of poly(ether urethane)s *in vivo*.[55] A later study found that *in vivo* stress cracking of this poly(ether urethane) was reproduced *in vitro* by treating pre-stressed polymer specimens with an oxidative medium (10% hydrogen peroxide with 0.10 M cobalt chloride).[56] The cobalt chloride catalyzes the decomposition of the hydrogen peroxide to form hydroxyl radicals, a form of ROS that attacks the polymer. Under these conditions simulating the isolated microenvironment between the surface of the biomaterial and the cell, *in vitro* stress cracking was similar in appearance to that observed *in vivo*. Furthermore, infrared spectroscopy showed that ROS participated in the oxidative degradation process.[57] Thus, oxidative degradation and environmental stress cracking have a synergistic effect on the failure of poly(ether urethane) catheter lead insulation, by which oxidative degradation drives the embrittlement of the polymer surface and its subsequent cracking, which in turn exposes new surfaces of the material to oxidative degradation and ultimately clinical device failure.[58] Similar to poly(ether urethane)s, PP is susceptible to oxidation, which results in chain scission, loss of ductility (e.g., embrittlement),[59] and degradation, such as pitting, peeling, and cracking[60]. Embrittlement occurs at a very low conversion in the chain scission process, and surface embrittlement of the PP fibers leads to crack initiation. Mechanical stress on the fibers will in turn enhance stress cracking and expose new PP surface to the oxidative environment. I have published two papers in the scientific journal *Biomaterials*, one in 2011 and one in 2014, using the same 20% H_2O_2 /0.1 M cobalt chloride system to measure the oxidative degradation rate of poly(ester urethane) and poly(thioketal urethane) scaffolds. Thus, this *in vitro* oxidative degradation test is well established in the scientific literat... me it developed the SUI and POP devices. Hov... er done.

Ethicon has also been made aware of the ... an implantable medical device through the Mate... ed that PP is incompatible with strong oxidizer ... is exposed to reactive oxygen species, which a... gn body reaction.

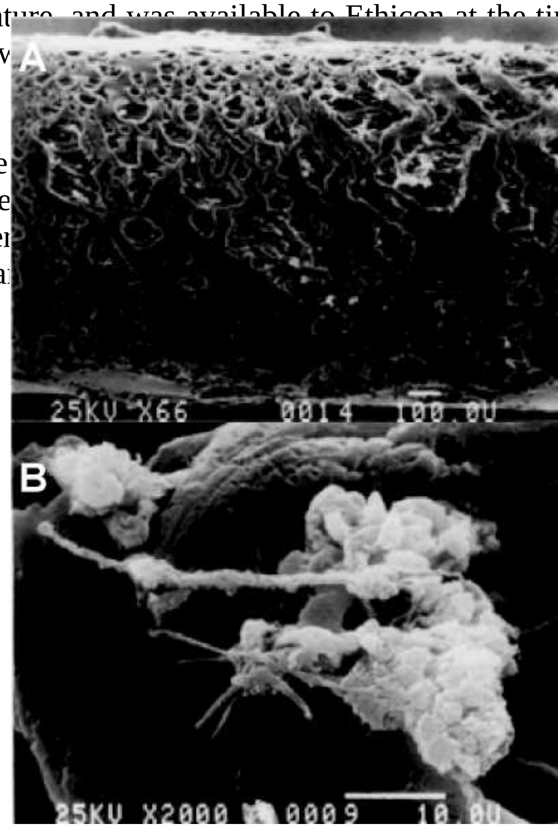

Figure 8. (A) SEM photograph of pre-stressed Pellethane 80A specimen implanted for 5 weeks. The specimen had severe cracking. Original magnification x66. (B) SEM photograph (at higher magnification) of pre-stressed Pellethane 80A specimen implanted for 5 weeks. Cellular adhesion was present. Original magnification x2000. From Zhao et al. JBMR 24:621, 1990.

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54 *Id.*

55 Zhao et al. JBMR 24:621, 1990.

56 Zhao et al. JBMR 27:379-89, 1993.

57 Wiggins MJ, Wilkoff B, Anderson JM, Hiltner A. Biodegradation of polyether polyurethane inner insulation in bipolar pacemaker leads. J Biomed Mater Res 2001;58(3):302–7

58 James M. Anderson1,2,*, Analiz Rodriguez1,*, and David T. Chang2. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.

59 Fayolle et al. Initial steps and embrittlement in the thermal oxidation of stabilized polypropylene films. Polym Degrad Stability 75:123-9, 2002

60 VV Iakovlev, ET Carey, J Steege. Pathology of Explanted Transvaginal Meshes. Int. J. Medical, Health, Pharmaceutical and Biomedical Eng. 8(9):510-513, 2014

61 ETH.MESH.05439518

The report from Mesh Repair of Uterovaginal Prolapse meeting in May 1997 noted that an ideal mesh would have lower density compared to that of the TVT to minimize the foreign body reaction.[62] Similar concerns were noted in a discussion document for the design of new mesh for prolapse repair, in which it was noted that the mesh used in the TVT is not the ideal material for anterior prolapse, and that the amount of foreign body should be minimized to reduce the risk of complications.[63]

The hernia literature also provides evidence that the foreign body reaction alters polypropylene *in vivo*. In a study evaluating non-degradable meshes explanted from 17 patients that had surgery for repair of abdominal wall defects, a foreign body reaction characterized by granulation tissue and inflammatory cells 3 – 24 months post-implantation was seen.[64] The PP meshes from this study showed more inflammatory cells and fibroblasts near the mesh interface when compared to PTFE and polyester.

Despite internal and published studies to the contrary, Ethicon documents further indicate that their sales force was instructed to "[r]eassure [surgeons] that PROLENE is proven to be inert and there are hundreds of papers going back 25 years to reinforce this point."[65] However, Daniel F. Burkley, a Principal Scientist at Ethicon, testified that in his 34 years at the company, he was only familiar with one study that was conducted regarding the changes that occurred due to oxidative degradation of explanted polypropylene suture or mesh.[66] Mr. Burkley also testified that this study showed that changes due to oxidation were still progressing after seven years of implantation.[67]

7) PP mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee; using heavy-weight mesh directly correlates to more PP being exposed to the foreign body reaction and greater changes after implantation, which increases the risk of complications.

The literature has confirmed that the properties of PP mesh change after implantation, causing adverse events like, pain, scarring and inflammation. In addition, Ethicon employees and consultants, both before and after the TVT was launched, have noted that heavy-weight meshes like the TVT comprise significantly more polypropylene than sutures or light-weight meshes, and therefore the foreign body reaction and resulting changes on the surface of the TVT device will be much greater than that for a lightweight mesh or a non-load bearing suture.[68] These findings are supported by the conclusions drawn by external consultants and Ethicon employees, as well as the available scientific literature reporting PP oxidation in response to cell-secreted ROS and complications associated with the mesh used in the TVT.[69]

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[62] Eth.Mesh.12006257
[63] Eth.Mesh.12009027
[64] Foreign Body Reaction to Meshes Used for the Repair of Abdominal Wall Hernias. U. Klinge,1,3 B. Klosterhalfen,2,3 M. Mu¨ller1 and V. Schumpelick1. Eur J Surg 1999; 165: 665–673
[65] ETH.MESH. 00865322
[66] Burkley Deposition 05/23/2013 P.312:23-313:24
[67] Burkely Deposition 05/23/2013 P.315:8-13
[68] Are Meshes With Lightweight Construction Strong Enough?; Jorge L. Holste*; ETHICON GmbH, R&D Europe, D-22841*, Norderstedt, Germany; J. Otto, E. Kaldenhoff, R. Kirschner-Hermanns, T. Muhl, U. Klinge. W.S. Cobb, K.W. Kercher, and B.T. Heniford.The Argument for Lightweight Polypropylene Mesh in Hernia Repair Surg Innov. Mar;12(1):63-9 (2005)
[69]Eth.Mesh.05479411, Eth.Mesh.07192929, Eth.Mesh.07192412.

More recently, Wood et al. published a comparison of three different explanted synthetic meshes (polypropylene, expanded polytetrafluoroethylene (ePTFE), and polyethylene terephthalate (PET)) from a single patient who had undergone three recurrent ventral hernia repairs.[70] Implantation times for the meshes were 3 years for the PP and PET meshes and 2 years for the ePTFE mesh. SEM images of explanted PP mesh "showed significant surface cracking" while the PET and ePTFE meshes did not. FTIR analysis also confirmed PP degradation from "free radical formation and oxidation of the polypropylene mesh while *in vivo."*

The Wood study supports the conclusions published by Clavé et al., which examined explanted pelvic meshes for degradation. Clavé reported that 42% of the explants showed evidence of chronic inflammation, characterized by an infiltrate of mononuclear cells and FGBCs. SEM analysis revealed that the implants were degraded, and that degradation was observed in meshes that had been implanted for at least 3 months.[71]

The findings of the Clavé study findings reinforced work done by Costello et al., who reported PP mesh oxidation and embrittlement as being a cause of mesh degradation and complications *in vivo*.[72] Costello derived his conclusions from comparisons made between pristine and explanted samples via molecular weight, SEM imaging, and compliance testing. Those authors reported that all three of these methods confirmed that PP mesh had degraded *in vivo*, most likely by oxidation.[73]

Another study investigated 14 explanted hernia mesh samples observed by SEM that 85% of the samples showed evidence of cracking, fissures, and peeling.[74] After host tissue was removed, the mesh samples remained folded and contracted, evidencing that mesh samples were permanently changed after implantation.

In a 2015 study I co-authored with Dr. Vladimir Iakovlev analyzing 164 explanted PP pelvic meshes, we reported the presence of adherent inflammatory cells expressing the oxidative enzyme myeloperoxidase, degradation of polypropylene, and micro-cracking near the surface of the polypropylene fibers. Degradation of explanted meshes was observed as early as 18 months.[75] Similar findings were reported by Mays et al., who observed oxidative degradation and transverse cracking of explanted PP pelvic mesh.[76]

Most importantly, these studies linked complaints of chronic pain and sclerosis to the foreign body reaction to implanted PP mesh and the consequent degradation and micro-

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[70] Wood, A.J., et al. *Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET hernia meshes from an Individual Patient*. J. MATER. SCI. MATER. MED. 24(4): 1113-1122 (2013).

[71] Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261-270

[72] Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov. 14:168–176 Costello CR, Bachman SL, Grant SA, Cleveland DS, Loy TS, Ramshaw BJ (2007); Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Costello CR, Bachman SL, Grant SA (2007) Res Part B: Appl Biomater 83B:44-49

[73] *Id.*

[74] Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater. Res Part B: Appl Biomater 83B:44-49

[75] VV Iakovlev, SA Guelcher, R Bendavid. In vivo degradation of polypropylene: microscopic analysis of meshes explanted from 130 patients. Journal of Applied Biomedical Materials Research B: Applied Biomaterials, 2015 Aug 28 doi: 10.1002/jbm.b.33502

[76] A Imel, T Malmgren, M Dadmun, S. Gido, J Mays. In vivo oxidative degradation of polypropylene pelvic mesh. Biomaterials 73:131-141, 2015.

cracking near the surface of PP fibers. These principles also apply to PP particles shed from the mesh during implantation, which is consistent with the testimony of Ethicon medical director Piet Hinoul that when particle loss occurs during implantation, the released particles result in inflammation that can cause pain.[77]

Large animal models, such as sheep, enable evaluation of PP mesh at longer time points and under conditions more representative of the clinical environment for SUI and POP repair.[78] A pilot study evaluated Prolene mesh implanted vaginally in sheep at 6 and 12 weeks.[79] The incidence of vaginal erosion was observed to be 33%. Macrophages and foreign body giant cells were also observed at 12 weeks. Two more recent studies have investigated differences between PP meshes implanted vaginally and abdominally using a sheep model.[80] PP mesh implanted vaginally showed more contraction and exposures, which are both mesh-related complications, than mesh implanted abdominally.[81] The authors further noted that the 15% incidence of vaginal exposures in all animals was comparable to that observed clinically, and found that mesh-related complications can be induced by vaginal mesh implantation. Contraction and folding, which have also been associated clinically with pain,[82] were also observed to be higher for vaginally implanted mesh compared to that implanted abdominally. In a follow-up study, the same authors investigated the effects of a collagen coating on mesh complications and made similar findings.[83] Vaginal exposures were observed in 33%, while no abdominal exposures were observed. Macrophages and foreign body giant cells were observed at 60 and 180 days in both vaginal and abdominal meshes. These findings led the authors to conclude that the sheep is an effective model to study complications of vaginal mesh. They further noted that the differential wound healing response and mechanical forces between the vaginal and abdominal wall environments may be responsible for the differences in mesh-related complications between the two implantation sites. Ethicon could have performed a similar sheep study at any time before or after the launch of its any of its mesh products to investigate the incidence of similar mesh-related complications. However, to my knowledge these studies have not been done.

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[77] Trial Testimony of Piet Hinoul, Batiste v. Ethicon, page 26-28

[78] Feola A, Endo M, Urbankova I, et al. Host reaction to vaginally inserted collagen containing polypropylene implants in sheep. Am J Obstet Gynecol 2015;212:474.e1-8.

[79] de Tayrac R1, Alves A, Thérin M.; Int Urogynecol J Pelvic Floor Dysfunct. 2007 May;18(5):513-20. Epub 2006 Aug 29.Collagen-coated vs noncoated low-weight polypropylene meshes in a sheep model for vaginal surgery. A pilot study.

[80] BJOG. 2013 Jan;120(2):244-50. doi:10.1111/1471-0528.12081. Graft-related complications and biaxial tensiometry following experimental vaginal implantation of flat mesh of variable dimensions. Manodoro S1, Endo M, Uvin P, Albersen M, Vláčil J, Engels A, Schmidt B, De Ridder D, Feola A, Deprest J. This study used Gynemesh M, which has polyglecaprone (not sure what this is) fibers that resorb; Am J Obstet Gynecol. 2015 Apr;212(4):474.e1-8. doi: 10.1016/j.ajog.2014.11.008. Epub 2014 Nov 8. Host reaction to vaginally inserted collagen containing polypropylene implants in sheep. Feola A, Endo M, Urbankova I, Vlacil J, Deprest T, Bettin S, Klosterhalfen B, Deprest J. This study used Bard meshes, one of which was coated with collagen.

[81] Deprest BJOG 2013

[82] Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn 2011;30:2–12.

[83] Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn 2011;30:2–12; Deprest AJOG 2015

Ethicon documents indicate that the company was aware of the Costello article in 2007, but never considered the effect of PP oxidation during these meshes design or product lifecycle. An Ethicon Medical Affairs employee, Tom Divilio, M.D., indicated that the Costello authors were "challenging our perception of polypropylene as an 'inert' material after implantation." He went on to note that "I think it's important that we understand what they are seeing as this group has a well-funded lab that will be looking at explanted mesh in great volume over the next couple of years and our current concepts are going to be challenged. Would appreciate it if we could think of some study designs that would confirm or refute their assumptions."[84] In 2012, Ethicon responded to a request by a British regulatory agency to explain how the 2010 publication by Clave et al impacts the performance of their products.[85] In this document, Ethicon noted "[we] are not aware of any findings that would impact the clinical performance of polypropylene monofilament"[86], and that "[p]olymers may be subject to surface degradation by these reactive species, the impact of which has not been clinically assessed."[87]

In summary, Ethicon scientists reported evidence of chronic inflammation, oxidation, and degradation (micro-cracking) of Prolene in preclinical studies and in human explants. These observations are consistent with the known susceptibility of polypropylene to oxidation outside the body, the known effects of the foreign body reaction on implanted biomaterials, and published studies on explanted PP mesh.[88] Despite the fact that Ethicon scientists recommended additional testing to confirm or exclude the oxidation mechanism, I have found no evidence that these tests (which were available to Ethicon during development of the SUI and POP devices) were performed. Consequently, the risks inherent to Prolene oxidation and degradation are detrimental to all of those who have been implanted with the SUI and POP devices.

[84] ETH.MESH. 05588123
[85] ETH.MESH. 07226481
[86] Id
[87] Id
[88] VV Iakovlev*, SA Guelcher, R Bendavid. In vivo degradation of polypropylene: microscopic analysis of meshes explanted from 130 patients. *Journal of Applied Biomedical Materials Research B: Applied Biomaterials*, In Press

FACTS OR DATA CONSIDERED IN FORMING OPINIONS

The opinions and the bases for those opinions are set forth above. In addition to my knowledge, skill training and experience as an engineer, the following depositions of Ethicon employees and the exhibits thereto were supplied to me: Cliff Volpe, Piet Hinoul, David Robinson, Sunny Rah, Aaron Kirkemo, Sean O'Bryan, Scott Ciarrocca, Vincenza Zaddem, Elizabeth Vailhe, Christophe Vailhe, Joerg Holste, Boris Batke, Daniel Burkley, Thomas Barbolt, Brigitte Hellhammer, Juergen Trzewik, Martin Weisberg, Axel Arnaud, Dan Smith, Prof Thomas Muehl, Dr. Bernd Klosterhalfen, Kevin Ong, Whenxin Zheng, Daniel Sexton, and Jeffrey Brent.

I have also considered the following material identified in Exhibit B.

In addition, the following reports were supplied to me: Dr. Howard Jordi, Dr. Russell Dunn, Prof Thomas Muehl, Prof. Bernd Klosterhalfen, Thomas Barbolt, Dr. Wenxin Zheng, and B. Todd Heniford, M.D. The findings of these experts are consistent with my opinions.

COMPENSATION

A fee sheet has been attached as Exhibit C.

LISTING OF CASES IN WHICH TESTIMONY HAS BEEN GIVEN IN THE LAST FOUR YEARS

- IN RE PELVIC MESH AMS LITIGATION, SERRANO ET AL – SEPTEMBER 2013
- IN RE PELVIC MESH ETHICON LITIGATION, HUSKEY ET AL. - MARCH 2014
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, ALBRIGHT ET AL – JULY 2014
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, CARDENAS ET AL – AUGUST 2014
- IN RE PELVIC MESH ETHICON LITIGATION, HUSKEY ET AL – AUGUST 2014
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, BARBA ET AL - FEBRUARY 2014
- IN RE PELVIC MESH BARD LITIGATION, CORRIVEAU ET AL – NOVEMBER 2014
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, FRANKUM ET AL – DECEMBER 2014
- IN RE PELVIC MESH ETHICON LITIGATION, PERRY - DECEMBER 2014

- IN RE PELVIC MESH ETHICON LITIGATION, PERRY – JANUARY 2015
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, BARBA ET AL - MAY 2015
- IN RE PELVIC MESH AMS LITIGATION, KILGORE ET AL - FEBRUARY 2015
- IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION, CARLSON – OCTOBER 2015

Scott Guelcher, Ph.D.
Guelcher Consulting, LLC